Radiotherapy and Oncology 162 (2021) 195–201

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

A multi-centre analysis of adjuvant contact X-ray brachytherapy (CXB) in rectal cancer patients treated with local excision – Preliminary results of the CONTEM1 study

Amandeep Dhadda [a,*], Arthur Sun Myint [b], Brice Thamphya [c], Iain Hunter [a], M. Hershman [d], Jean-Pierre Gerard [c]

[a] Queen's Centre for Oncology & Haematology, Hull University Teaching Hospitals NHS Trust, Hull; [b] Clatterbridge Cancer Centre, Liverpool, United Kingdom; [c] Service de Radiotherapie, Centre Antoine-Lacassagne, Nice, France; [d] Medecho, London, United Kingdom

ARTICLE INFO

Article history:
Received 4 November 2020
Accepted 19 July 2021
Available online 27 July 2021

Keywords:
Rectal cancer
Brachytherapy
Papillon
Local excision

ABSTRACT

Introduction: Early rectal cancers are increasingly diagnosed through screening programmes and are often treated using local excision (LE). In the case of adverse pathological features completion total mesorectal excision surgery (TME) is the standard recommendation. The morbidity and mortality risks of TME have stimulated the use of adjunctive treatments following LE to achieve organ preservation.

Material and methods: Patients treated with adjuvant CXB following local excision between 2004 and 2017 in three centres were identified (Clatterbridge, Hull, Nice). All patients had adverse pathological features including: lymphovacular invasion, Sm2-3 Kikuchi level, tumour budding, pT2, positive resection margins (R1). CXB was performed with the Papillon50 [tm] machine to a dose of 40–60 Gy in 2 or 3 fractions over 2–4 weeks preceding/following external beam chemo/radiotherapy. Kaplan Meier survival estimates were used for outcomes measures.

Results: 194 patients were identified. Median age was 70 years. pT staging was: pT1:143, pT2:45, pT3:6. CXB alone was given in 24 pts and combined with EBRT in 170. Median follow-up time was 77 months (range 7–122 months). Local relapse rate was 8% and distant metastases 9%. Organ preservation was achieved in 95%. 6 year local recurrence free and overall survival was 91% and 81% respectively. Cancer specific survival was 97%. No treatment related mortality was seen.

Conclusion: This large multi-centre cohort study using adjuvant CXB following local excision suggests excellent oncological outcomes for these patients without completion TME. This treatment approach can be considered as an alternative for selective patients compliant with long term follow up.

Total mesorectal excision (TME) has been the gold standard surgical treatment of rectal cancer for several decades with low rates of local recurrence. Neo-adjuvant chemo/radiotherapy is used in conjunction for selected cases to reduce local recurrence risks with no additional benefit seen on overall survival [1–3]. There is now an increasing awareness of the long term morbidity of TME surgery as well elevated mortality risks in elderly patients [4,5]. As a consequence alternative approaches have been explored to reduce these anticipated risks and increase organ preservation including local excision [6].

As a result of the introduction of national screening programmes there has been an increase in the number of very early rectal cancers being diagnosed [7]. Due to these factors, local excision of small early rectal cancers is now increasing although as a single modality for patients with pT2 rectal cancer this would still amount to an oncological compromise [8]. Some of these are also diagnosed inadvertently following endoscopic excision of assumed benign rectal polyps. Patients with adverse pathological features following local excision are normally offered completion TME surgery as the gold standard approach to allow pathological assessment of mesorectal nodal involvement. There is ongoing uncertainty about the long term outcomes of alternative approaches which avoid completion TME in such patients including adjuvant radiotherapy.

Contact X-ray brachytherapy (CXB) as described by Papillon using 50 kVp X-rays has been shown in several case series to provide excellent local recurrence and disease free survival rates for selected patients without surgery [9–11]. We present our multicentre series of rectal cancer patients treated with local excision

* Corresponding author at: Queen's Centre for Oncology & Haematology, Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Castle Road, Cottingham, Hull, United Kingdom.
E-mail address: Amandeep.Dhadda@nhs.net (A. Dhadda).

https://doi.org/10.1016/j.radonc.2021.07.021
0167-8140/

and adjuvant external beam mesorectal chemo/radiotherapy and CXB using a standardised approach.

Methods

Patients treated with local excision and adjuvant CXB, due to adverse pathological features, at Clatterbridge Cancer Centre, Liverpool; the Queen's Centre for Oncology and Haematology, Hull and Centre Antoine Lacassagne, Nice between 2004 and 2017 were identified. All patients had staging to exclude metastatic disease and were treated as per the CONTEM 1 protocol which has been previously described [12].

All patients included were counselled that TME constituted gold standard therapy. Local treatment was reserved for patients refusing radical surgery due to the need for a permanent stoma or for those with prohibitive operative risks from radical surgery relating to pre-existing medical co-morbidities. Adverse pathological factors following local excision included lymphovascular invasion (LVI), SM2-3 Kikuchi level, tumour budding, pT2 and involved or unknown resection margins (R1/Rx).

The majority of patients (84%) were treated with CXB to a dose of 60 Gy in 2 fractions to the site of local excision followed/preceded in most cases by external beam (chemo)/radiotherapy to the pelvis to treat potentially involved occult mesorectal nodes. External beam radiotherapy volumes were confined to treat the mesorectum and generally did not go above S2/3. No adjuvant chemotherapy was routinely given after radiotherapy treatment.

CXB was performed in an outpatient setting. Enemas were given prior to the procedure to clear the rectum cavity with topical local anaesthetic (lidocaine 2%) gel and glycerol trinitrate cream applied around the anal canal for patient comfort. All patients treated using the Arianne Papillon 50 machine using 50 kVp X-rays. Treatment fractions were separated using 2 week intervals.

Following completion of treatment patients were followed up with regular MRI of the pelvis, digital rectal examination and rectoscopy. These were repeated at 3–6 monthly intervals with 12 monthly CT scans performed to screen for distant disease for the first 24 months. Two colonoscopies were performed during the first 5 years of follow up. Annual rectoscopy was performed annually after 5 years.

Statistical methods

Statistical analysis was performed using the R 3.6.1 software. Qualitative data were presented as absolute frequency, relative frequency and percentage of missing data. The data were compared using Chi-square or a Fisher exact test in the case of failure to meet the Chi-square application rules. Quantitative data were compared using the Student T test or the Wilcoxon test.

Censored data (survival data) were defined between the date of local excision and the date of event, lost-of-follow-up patients were censored at last known date of contact. Kaplan–Meier regression analysis was performed for local recurrence, disease free survival and overall survival. Multi-variate Cox regression analysis was used to explore prognostic covariates.

Results

Between 2004 and 2017 a total of 194 patients were treated using the schedule and technique described above. The median age of patients was 69 years (range 36–91 years) with other demographics shown in Table 1. Median follow up was 77 months (range 7–122 months). The majority of patients (73.7%) of patients had pT1 tumours (143/194) with 26.3% of patients having pT2/3 tumours (51/194). Most patients had CXB followed/preceded by external beam chemoradiotherapy to treat the mesorectum (107/194, 55.1%). In patients who were considered unfit for chemoradiotherapy due to underlying co-morbidities mesorectal external beam radiotherapy was used in conjunction with CXB in 63 (32.5%) patients (35 patients 45–50 Gy in 25 fractions, 28 patients 25 Gy in 5 fractions) with 24 (12.4%) patients having CXB alone.

Table 1
Demographic/pathological characteristics of patients (pT = pathological T stage; Margin R0 = clear, R1 = microscopically involved, Rx = unknown; SM = Kikuchi submucosal level in pT1 tumours; LVI = lympho-vascular invasion).

SITE	Clatterbridge	Hull	Nice	TOTAL
SEX				
Female	47 (36.7%)	8 (22.9%)	13 (41.9%)	68 (35.1%)
Male	81 (63.3%)	27 (77.1%)	18 (58.1%)	126 (64.9%)
AGE				
<75	87 (68%)	24 (68.6%)	24 (77.4%)	135 (69.6%)
>=75	41 (32%)	11 (31.4%)	7 (22.6%)	59 (30.4%)
pT				
pT1	99 (77.3%)	16 (45.7%)	28 (90.3%)	143 (73.7%)
pT2	24 (18.8%)	18 (51.4%)	3 (9.7%)	45 (23.2%)
pT3	5 (3.9%)	1 (2.9%)	0 (0%)	6 (3.1%)
pT_Regroup				
pT1	99 (77.3%)	16 (45.7%)	28 (90.3%)	143 (73.7%)
pT2/pT3	29 (22.7%)	19 (54.3%)	3 (9.7%)	51 (26.3%)
Margin				
R0	53 (41.4%)	13 (37.1%)	21 (67.7%)	87 (44.8%)
R1	49 (38.2%)	20 (57.1%)	9 (29.0%)	78 (40.2%)
Rx	26 (20.3%)	2 (5.7%)	1 (3.2%)	29 (15.0%)
SM				
Missing	47 (47.5%)	0 (0%)	13 (46.4%)	60 (42.0%)
SM1	7 (7.1%)	2 (12.5%)	1 (3.6%)	10 (7.0%)
SM2	16 (16.2%)	7 (43.8%)	9 (32.1%)	32 (22.4%)
SM3	29 (29.3%)	7 (43.8%)	5 (17.9%)	41 (28.6%)
LVI				
Missing	128 (100%)	0 (0%)	0 (0%)	128 (66.0%)
No	0 (0%)	16 (45.7%)	29 (93.5%)	45 (23.1%)
Yes	0 (0%)	19 (54.3%)	2 (6.5%)	21 (10.8%)

Crude local relapse with a median follow up of 77 months was 7.7% (15/194) with distant metastases being 9.3% (18/194). There were no statistical differences between the centres for outcomes (Fig. 1). Organ preservation was achieved in 95% of patients. Local recurrence free, overall and cancer specific survival is shown in

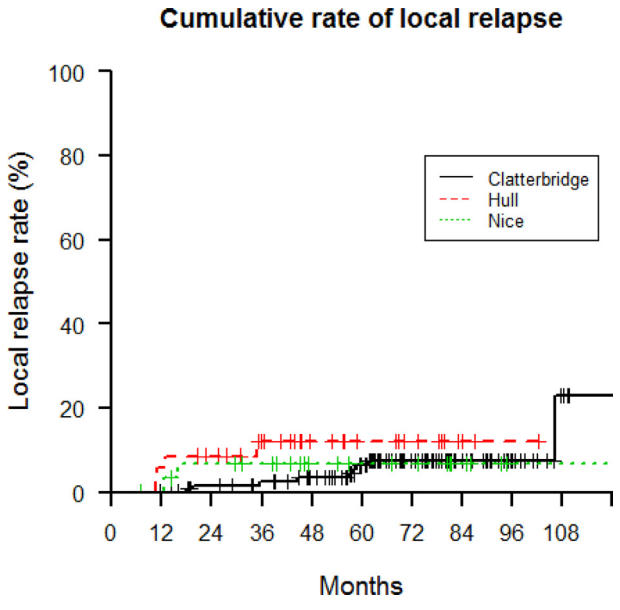


Fig. 1. Rate of local relapse between centres over time.

Figs. 2–5. Kaplan Meier estimated local relapse rate at 6 years was 9% (CI 95: 4–13) with overall survival being 81% (CI 95: 75–87). Most of these were non-cancer deaths with 6 year cancer specific survival being 97%. No treatment related mortality was seen.

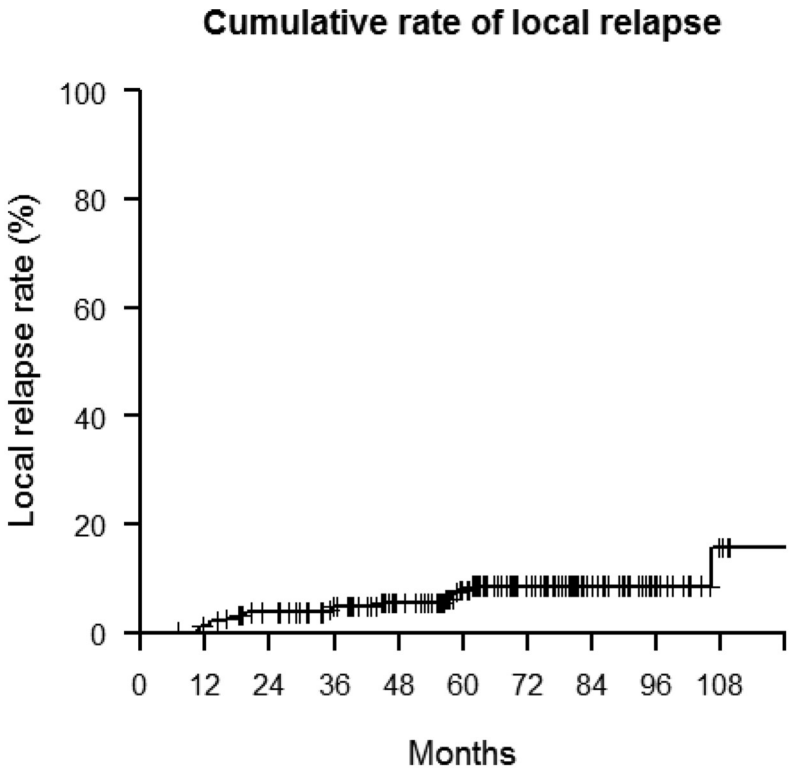
Due to the small number of events only a few prognostic parameters were observed. Lympho-vascular invasion (LVI) was associated with an increased risk of local relapse (4% vs 19% out of 66 patients with LVI reported $p = 0.08$) Local relapse was also associated with a higher risk of distant metastases (6.6% vs 40%, $p < 0.001$). Although most of the local relapses were within the first 2 years (7/15) (Fig. 2) some relapses were seen at later time points and even at 9 years post treatment suggesting these patients need prolonged follow up.

The sequence of adjuvant treatment did seem to be important with patients who had CXB prior to external beam chemo/radiotherapy showing lower local recurrence rates of 4.5% (6/134) vs 15% (9/60) which was statistically significant on multi-variate analysis ($p = 0.037$). Sex also seemed to be linked to outcomes with females showing lower distant metastases rates of 1.4% (1/68) than males of 13.4% (17/126, $p = 0.04$) but with a pathologically worse group in males compared to females (pT2/3 31% vs 18%).

Discussion

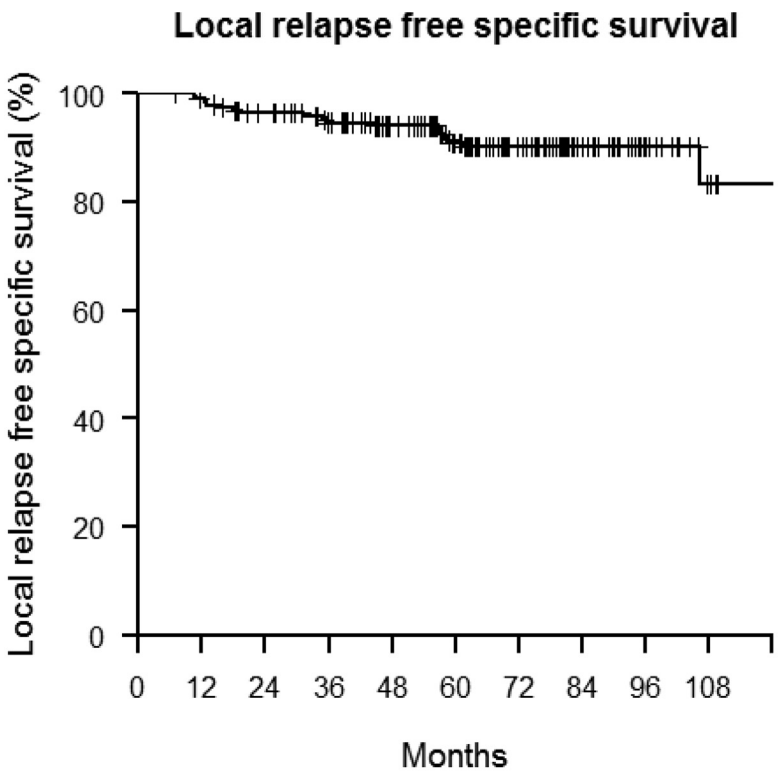
This is the first multi-centre analysis of a cohort of patients treated with local excision and adjuvant contact brachytherapy to be reported. All patients treated in the series had features associated with an elevated risk of local recurrence with local excision alone including: tumour size, Kikuchi SM2/3, pT2, lympho-vascular invasion, involved surgical margins which required further adjuvant treatment. The local relapse rate of 9% at 6 years with long term follow up compares favourably with previously published data including a recently published large case series of 180 patients [13]. However, it has limitations in that it does not provide randomisation to other treatment strategies such as external beam chemo/radiotherapy alone or even surveillance. Nor is it complete with all pathological factors such as lympho-vascular invasion being available in all cases or uniform in the types of local excision performed and adjuvant external beam radiotherapy received. Despite this, it provides long term outcome data to inform patients on a strategy to avoid radical TME and potentially achieve high rates of organ preservation.

The management of early rectal cancer is becoming increasingly complicated with various treatment strategies being employed to



time	0	24	48	72	96	120
n.risk	194	177	139	81	23	8
n.event	0	7	3	4	0	1
n.censor	0	10	35	54	58	14
local relapse rate	0	0.04	0.05	0.09	0.09	0.16
lower	0	0.01	0.02	0.04	0.04	0.01
upper	0	0.06	0.09	0.13	0.13	0.28

Fig. 2. Combined local relapse rate over time for rectal cancer patients treated with local excision and adjuvant contact X-ray brachytherapy.



time	0	24	48	72	96	120
n.risk	194	177	139	81	23	8
n.event	0	7	4	5	0	1
n.censor	0	10	34	53	58	14
surv	1	0.96	0.94	0.9	0.9	0.83
lower	1	0.94	0.91	0.86	0.86	0.71
upper	1	0.99	0.98	0.95	0.95	0.98

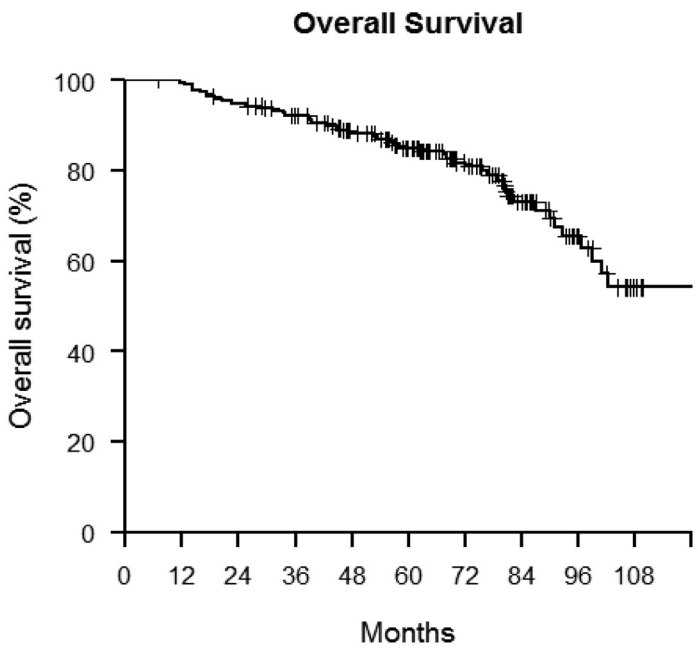
Fig. 3. Combined local recurrence free survival over time for rectal cancer patients treated with local excision and adjuvant contact X-ray brachytherapy.

avoid TME surgery in selected patients including, local excision, external beam radiotherapy and contact brachytherapy (CXB), either as single modality or multi-modality therapy. None of these have been compared directly against TME but have been utilized as an avenue to avoid the long term morbidity and mortality risks of surgical treatment. This is increasingly relevant with ageing populations across the world with the associated risks from radical surgical treatment increasing with age [5]. With national screening programmes for colorectal cancer established in many countries, an increasing number of very early rectal cancers are being discovered. Whether these can be treated as effectively with less aggressive treatments is certainly an interesting point although at the moment there remains a lack of randomized trial data. Real world case series data as we have presented provide some insight into outcomes that can potentially be achieved in patients who opt not to have radical surgery following a local excision or are considered unfit for such surgery.

The TESAR trial is hoping to provide the much needed randomized evidence for patients having local excision upfront for rectal cancer [14]. Patients will be randomised following local excision to adjuvant chemoradiotherapy or TME surgery with the primary endpoint being 3 year local recurrence free survival. It will be interesting to see if patients would be willing to participate in this study and agree to a randomization involving TME surgery over an organ preservation approach.

A meta-analysis of oncological outcomes after local excision of pT1-2 tumours requiring adjuvant chemoradiotherapy or completion surgery suggested a local recurrence rate of 14% vs 7% respectively [15]. The weighted local recurrence for pT1 tumours was 10% and for pT2 tumours was 15%. A review from the SEER database of pT2 patients treated with local excision alone confirmed poor outcomes for this group as a standalone treatment with 5 year cancer specific survival being 70% [16]. The addition of adjuvant radiotherapy seemed to result in more favourable outcomes with 5 year cancer specific survival being 78% which was statistically similar to local excision followed by radical surgery. A case series of 93 patients with pT1-3 rectal cancers treated mainly with transanal excision and adjuvant radiotherapy estimated a local recurrence rate at 5 years of 14% [17].

Our outcome data compares very favourably with these publications with the potential discriminator being the addition of a contact brachytherapy boost to the site of excision in our cohort. The benefits of this in view of the depth dose characteristics of 50 kVp X-rays would realistically be in reducing luminal recurrence at the site of excision with the external beam radiotherapy affecting mesorectal recurrence rates. The sequencing of the CXB



time	0	24	48	72	96	120
n.risk	194	182	147	89	25	9
n.event	0	10	12	10	11	4
n.censor	0	2	23	48	53	12
surv	1	0.95	0.88	0.81	0.65	0.54
lower	1	0.92	0.84	0.75	0.56	0.42
upper	1	0.98	0.93	0.87	0.76	0.69

Fig. 4. Overall survival of rectal cancer patients treated with local excision and adjuvant contact X-ray brachytherapy.

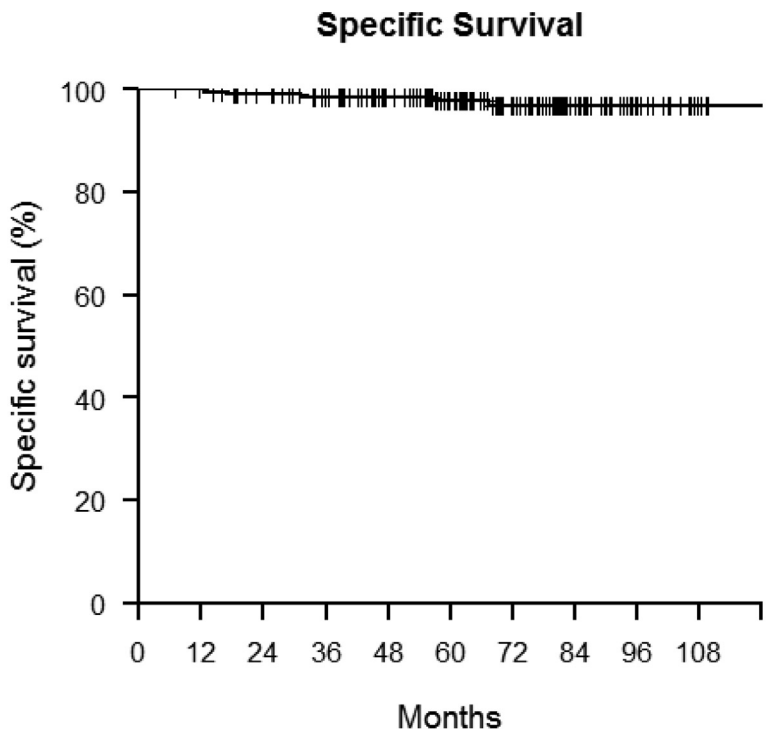
in our series seems important with local recurrence rates being 4% if given prior to external beam chemo/radiotherapy vs 15% if given after. There is uncertainty as to the reason for this and may well include overall treatment time or immunological factors but it would seem clear that if using this approach it would be reasonable to proceed with CXB prior to external beam chemo/radiotherapy. With our data suggesting that local recurrence is highly associated with distant metastases achievement of optimal local control which CXB may additionally offer may well be clinically relevant. Ideally this should be further investigated in a randomized controlled trial exploring the additional benefits of CXB over external beam radiotherapy, or vice versa, in this group of patients. It is also clear that there are potentially more late relapses beyond 2 years in comparison to the international watch and wait data in rectal cancer patients showing a complete clinical response to neoadjuvant chemo/radiotherapy suggesting these patients need more prolonged follow up than has traditionally been offered [18]. It is difficult to conclude whether these represent true late local recurrences or potentially new primary rectal cancers from our data.

Although completion TME surgery is the recommended course of action as the standard approach following local excision of a rectal cancer with adverse features it is common for the resection specimen to contain no residual disease. As a consequence, apart from the certainty of the pathology there are a large group of patients who may go through potentially life changing surgery with its associated complications with no long term benefits. Whether a more tailored approach could be adopted with adjuvant radiotherapy and surgery for local relapse for lower risk patients would seem to be a challenging but important conundrum. With patient choice and a discussion of potential treatment options an important tenet of modern medicine completion TME should not be a reflex action in these cases as it is accepted that patients must be informed of the various treatment options and their likelihood of success. The outcomes and risks that a patient considers appropriate may vary individually to a great degree and should always be considered in shared decision making [19].

The initial assessment of early rectal polyp cancers is also in need of improvement and the UK Pelican group has run a nationwide programme of SPECC (specialist polyp and early rectal cancer) workshops to improve knowledge and standardize approaches across multi-disciplinary teams. Recent work on multi-modal endoscopic assessment may further help in tailoring treatments for patients at the very earliest stage of diagnosis [20]. It is also vital these patients are then discussed in specialized early rectal cancer multi-disciplinary team meetings to plan their management.

Conclusion

The optimal approach for early rectal cancers remains to be clearly defined. This study provides evidence of excellent long term oncological outcomes of patients treated with local excision followed by adjuvant contact X-ray brachytherapy and should be considered as an alternative approach for patients considered unfit for or not accepting completion radical surgery. Patients



time	0	24	48	72	96	120
n.risk	194	182	147	89	25	9
n.event	0	2	1	2	0	0
n.censor	0	10	34	56	64	16
surv	1	0.99	0.98	0.97	0.97	0.97
lower	1	0.98	0.97	0.94	0.94	0.94
upper	1	1	1	1	1	1

Fig. 5. Cancer specific survival in rectal cancer patients treated with local excision and adjuvant contact X-ray brachytherapy.

accepting such an approach need to be counseled on the need for prolonged participation in established surveillance programmes to ensure local recurrences are picked up and salvaged at an early stage.

Conflicts of interest statement

None to declare.

References

[1] Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre randomised trial. Lancet 2009;373:811–20.
[2] van Gijn W, Marijnen CAM, Nagtegaal ID, Kranenbarg E-K, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12 year follow-up of the multicentre randomised controlled TME trial. Lancet Oncol 2011;12:575–82.
[3] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
[4] Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008;9:494–501.
[5] Giandomenico F, Gavaruzzi T, Lotto L, Del Bianco P, Barina A, Perin A, et al. Quality of life after surgery for rectal cancer: a systematic review of comparisons with the general population. Exp Rev Gastroenterol Hepatol 2015;9:1227–42.
[6] Gollins S, Moran B, Adams R, et al. Association of coloproctology of Great Britain & Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017) – multidisciplinary management. Colorectal Dis 2017;19:37–66.
[7] UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstation pilot of screening for colorectal cancer in the United Kingdom. BMJ 2004;329:133.
[8] Stitzenberg KB, Sanoff HK, Penn DC, Meyers MO, Tepper JE. Practice patterns and long-term survival for early-stage rectal cancer. J Clin Oncol 2013;31:4276–82.
[9] Papillon J. Present status of radiation therapy in conservative management of rectal cancer. Radiother Oncol 1990;17:275–83.
[10] Gerard JP, Romestaing P, Chapet O. Radiotherapy alone in the curative treatment of rectal cancer. Lancet Oncol 2003;4:158–66.
[11] Sun Myint A, Grieve RJ, McDonald AC, Levine EL, Ramani S, Perkins K, et al. Combined modality treatment of early rectal cancer – the UK experience. Clinical Oncol 2007;19:674–81.
[12] Lindegaard J, Gerard JP, Sun Myint A, Myerson R, Thomsen H, Laurberg S. Whither Papillon? – Future directions for contact radiotherapy in rectal cancer. Clin Oncol 2007;19:738–41.
[13] Smith F, Pritchard D, Wong H, et al. A cohort study of local excision followed by adjuvant therapy incorporating contact X-ray brachytherapy boost instead of radical resection in 180 patients with rectal cancer. Colorectal Dis 2019;21:663–70.
[14] Bortslap W, Tanis P, Koedam T, et al. A multi-centre randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer. BMC Cancer 2016;16:513.
[15] Bortslap W, Coeymans T, Tanis P, et al. Meta-analysis of oncological outcomes after local excision of pT1-2 rectal cancer requiring adjuvant (chemo) radiotherapy or completion surgery. BJS 2016;103:1105–16.
[16] Wang XJ, Chi P, Zhang YY, Lin HM, Lu XR, Huang Y, et al. Survival outcome of adjuvant radiotherapy after local excision for T2 early rectal cancer: an

analysis based on the surveillance, epidemiology and end result registry database (SEER). Eur J Surg Oncol 2018;44:1865–72.
[17] Rackley T, Ma R, Brown C, et al. Transanal local excision for patients with rectal cancer: can radiation compensate for what is perceived as a non-definitive surgical approach? Dis Colon Rectum 2016;59:173–8.
[18] van der Valk M, Hilling D, Bastiaannet E, et al. Long term outcomes of clinical complete responders after neo-adjuvant treatment for rectal cancer in the International Watch and Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391:2537–45.
[19] Chan S, Tulloch E, Cooper E, et al. Montgomery and informed consent: where are we now? BMJ 2017;357.
[20] Emmanuel A, Lapa C, Ghosh A, et al. Multi-modal endoscopic assessment guides treatment for rectal early neoplastic tumours. Dis Colon Rectum 2020;63:326–35.